

Chronic urticaria and osteoporosis: a longitudinal, community-based cohort study of 11 944 patients*

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Summary

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Background Chronic urticaria (CU) carries many risk factors for osteoporosis, but data on the relationships between CU and osteoporosis are lacking.

Objectives To evaluate the association between CU and osteoporosis in a large community-based study.

Methods A nationwide observational longitudinal cohort study was conducted. CU was defined as four pairs of urticaria diagnoses; each pair was recorded within a period of 6 weeks and was registered by physicians in a primary-care setting. Patients with CU and their age- and sex- matched controls were followed for the incidence of osteoporosis and other laboratory data between 2002 and 2017. Data regarding systemic steroid exposure and other relevant risk factors for osteoporosis were obtained. Analyses of risk for osteoporosis were performed in Cox regression models adjusted for age, sex, exposure to systemic corticosteroids, obesity, smoking and hyper- and hypothyroid disease.

Results The study included 11 944 patients with CU and 59 829 controls. During the study's observation period, 1035 (8.7%) patients with CU were diagnosed with osteoporosis, compared with 4046 (6.8%) controls. The adjusted multivariate analysis demonstrated that CU was significantly associated with a higher risk for osteoporosis (hazard ratio 1.23, 95% confidence interval 1.10–1.37, $P < 0.001$).

Conclusions CU may impose a risk for osteoporosis. Appropriate targeted screening should be considered.

What's already known about this topic?

- Chronic urticaria (CU) is associated with the chronic inflammatory process.

What does this study add?

- In this nationwide cohort study, we determined that patients with CU had an increased risk for osteoporosis compared with the general population in Israel.

Chronic inflammation is a known risk factor for other inflammatory-driven medical conditions, such as obesity, hypertension, metabolic syndrome and osteoporosis. Chronic urticaria (CU) is being increasingly associated with low-grade chronic inflammation. Several inflammatory markers, cytokines and biomarkers were found to be increased in patients with CU.^{1,2} CU was also observed to be associated with increased serum lipids and fatty acids,³ hyperlipidaemia⁴ and metabolic syndrome.⁵ Recently, we observed an association between CU and metabolic syndrome and its components in a large, community-based cross-sectional study. Therefore, the concept of CU as a chronic inflammatory state is not unfounded.⁶

Osteoporosis is a chronic, debilitating disease that mostly affects patients over 50 years old. Once a diagnosis of osteoporosis is made, treatment hardly ever reverses patients' bone density back to its baseline. Therefore, the best treatment option for osteoporosis is early prevention by determining the primary risk factors coupled with early treatment. Although CU is now recognized as being associated with chronic inflammation, data on its association with osteoporosis are lacking. Therefore, the evaluation of CU as a risk factor for osteoporosis is clearly warranted.

This study aimed to investigate the association between CU, osteoporosis and the relevant risk factors, namely, vitamin D deficiency, hypercalcaemia, hypocalcaemia and hyperparathyroidism, in a community-based study utilizing the large medical database of Clalit Health Services (CHS).

Patients and methods

CHS is the largest healthcare provider organization in Israel and the second largest in the world. It serves about 4 500 000 enrollees. CHS has a comprehensive computerized database with continuous real-time input from pharmaceutical, medical and administrative operating systems. The registry is subjected to a constant validation process based on the repeated evaluation of diagnoses made by CHS physicians, registered prescriptions, pharmacy claims, laboratory tests and auxiliary tests for each patient. Comparison among diagnoses, drug administration, laboratory tests and auxiliary tests from various healthcare sources is performed repetitively, and inconsistencies in different records are resolved after authentication by the registry manager. The accuracy of the CHS Chronic Disease Register has been published.⁷ Our study was designed as a longitudinal, community-based cohort study of patients with CU from the CHS database with age- and sex-matched controls.

In CHS, consultation by specialists – dermatologists or allergologists – can be performed in three different types of setting: (i) inpatient (hospitalization, or emergency room visit without hospitalization); (ii) outpatient (the outpatient clinic is affiliated with a hospital) or primary care, where the consultation is performed by a board-certified specialist; and (iii) outside the hospital setting with no affiliation to any hospital. The last type is also referred to as the community setting.

Most of the patients included in the present study were diagnosed in the CHS community setting.

Case definition

We used a highly conservative definition for CU, stating that each patient must have had four pairs of urticaria diagnoses; each pair was recorded within a period of 6 weeks and was registered by physicians in a primary-care setting. Each urticaria diagnosis was made by a physician in a community services outpatient clinic or during hospitalization between January 2002 and December 2017. As we previously reported, CU diagnosis was validated with a manual search process performed in a randomly selected sample of files. In this manual search, we demonstrated a positive predictive value > 90%.^{6,8}

A control group of up to five control patients per case was selected and matched randomly by age and sex. Age matching was based on the exact year of birth (1-year strata). Controls were verified to be alive and contributing data to CHS on the date of the diagnosis of the matched case. The date of enrolment of the control participant was identical to the date of diagnosis of the matched case. The study population was followed until 31 December 2017 or until emigration, death or occurrence of the primary end point, whichever occurred first. Patients with one or more diagnosis of urticaria were excluded from the control group.

To avoid other significant causes of osteoporosis in our study population, patients who were ever diagnosed with one or more of the following diagnoses were excluded: hyper- and hypoparathyroid disease, chronic renal failure, alcohol abuse, drug abuse, cystic fibrosis, Crohn disease, ulcerative colitis, cirrhosis, Cushing syndrome, Addison syndrome, hyperprolactinaemia, hypophyseal adenoma, hypophyseal dysfunction, any organ transplantation and any malignancy.

In CHS, osteoporosis was diagnosed using dual-energy X-ray absorptiometry tests to determine the bone mineral density of the hip and spine. A T-score < 2.5 SDs from the age, sex and race/ethnicity average scores established the diagnosis of osteoporosis as previously described.

The demographic data that we obtained for the study population included age, sex, socioeconomic status, ethnicity, Charlson Comorbidity Index (a validated method for classifying comorbid conditions that may alter the risk of mortality),⁹ smoking status, body mass index, obesity and systemic steroid exposure. The patients' socioeconomic status was determined by the average socioeconomic status of the clinics in the area where each enrollee was registered. The clinics were classified as 1 (low), 2 (intermediate) or 3 (high). Patients were considered smokers if they had an active smoking diagnosis in the CHS chronic disease register. Patients with at least two consecutive prescriptions of systemic steroids were considered to be under steroid exposure.

Data on the blood tests performed during the study observation period were extracted and examined for parathyroid hormone (PTH), vitamin D, calcium, albumin and IgE serum levels. The mean values for these levels were calculated for

each patient, and peak and minimal values were obtained. Vitamin D deficiency was confirmed when the mean vitamin D serum levels were $< 30 \text{ ng dL}^{-1}$, hyperparathyroidism when the mean PTH serum levels were $> 60 \text{ pg dL}^{-1}$, hypocalcaemia when the mean calcium serum levels were $< 8 \text{ g dL}^{-1}$, hypercalcaemia when the mean calcium serum levels were $> 11 \text{ g dL}^{-1}$, and hypoalbuminaemia when the mean albumin serum levels were $< 3.5 \text{ g dL}^{-1}$.

Statistical analysis

Statistical analysis was performed using SPSS version 23 (IBM, Armonk, NY, U.S.A.). The data analysis consisted of comparing variables using t-tests, and dichotomous variables were appropriately compared using Pearson's χ^2 -test.

The baseline demographic characteristics and the mean serum levels (PTH, vitamin D, calcium, albumin and IgE) were compared between the patients with CU and the controls, and between the subgroups of patients with both osteoporosis and CU and patients with osteoporosis without CU. We used Kaplan–Meier analysis to obtain descriptive (unadjusted) data regarding the incidence of osteoporosis and the temporal relationships between CU and osteoporosis. Data on the incidence of hyperparathyroidism, hypocalcaemia, hypercalcaemia and hypoalbuminaemia were also obtained. Analysis of osteoporosis risk was performed in a multivariate Cox regression model using calendar time as the time scale and adjusting for possible confounders, including age, sex, exposure to systemic corticosteroids, obesity, smoking and hyper- and hypothyroid disease.

To address the possibility of a persistent residual confounding effect by corticosteroids we conducted an additional stratified analysis where we looked only at patients who had never received any systemic corticosteroids (oral, inhaled, injection etc.). To explore our dataset for surveillance bias, we performed a sensitivity analysis with a negative end point that is not associated with CU: syphilis. Analysis of syphilis risk among patients with CU vs. controls was performed. All variables were handled as binary variables in the analysis, except for age, which was classified as a continuous variable. A P-value < 0.05 was considered statistically significant.

This study was approved by the institutional review board of the Meir Medical Center, Kfar Saba, Israel (approval number 0003-2-com). It was exempted from the need for signed informed consent forms.

Results

In total 14 009 patients with CU and 67 478 controls were extracted from the CHS database. Following the exclusion of 2065 patients with CU and 7654 controls, the study included 11 944 patients with CU and 59 829 controls, with a total of 518 681 patient-years of follow-up. The baseline characteristics of the study population are presented in Table 1. Patients with CU had higher rates of high and intermediate socioeconomic status, lower rates of low socioeconomic status, and higher rates of obesity, diabetes and hypertension than the control group. The patients with osteoporosis and CU were younger and more likely to be male than the osteoporotic patients without CU. Table 2 presents the mean values of the

Table 1 Baseline characteristics of the study population

Cohort total	Patients with CU n = 11 994	General population n = 59 829	Osteoporosis with CU n = 1035	Osteoporosis without CU n = 4046
Age (years), mean $\pm$ SD	39.2 $\pm$ 21.5	39.4 $\pm$ 21.4	64.0 $\pm$ 12.2	64.9 $\pm$ 11.2
Sex, n (%)				
Female	8031 (67.2)	40 252 (67.3)	943 (91.1)	3768 (93.1)
Male	3913 (32.8)	19 577 (32.7)	92 (8.9)	278 (6.9)
Socioeconomic status, n (%) ^a				
Low	5139 (42.8)	25 839 (43.2)	361 (34.9)	1320 (32.6)
Medium	4727 (39.4)	23 549 (39.4)	465 (44.9)	862 (21.3)
High	1964 (16.4)	9691 (16.2)	203 (19.6)	310 (16.2)
Smoking, n (%)	3762 (31.5)	17 400 (29.1)	266 (25.7)	1067 (26.4)
Ethnicity ^b				
Arabic	2853 (23.9)	14 350 (24.0)	97 (9.4)	326 (8.1)
Non-Arabic	9091 (76.1)	45 479 (76.0)	938 (90.6)	3720 (91.9)
Charlson score, mean $\pm$ SD ^c	2.19 $\pm$ 2.7	2.03 $\pm$ 2.6	5.1 $\pm$ 2.5	5.0 $\pm$ 2.5
BMI (kg m^{-2}), mean $\pm$ SD ^d	26.16 $\pm$ 7.72	26.4 $\pm$ 9.31	27.3 $\pm$ 5.5	27.2 $\pm$ 6.3
Obesity	3251 (26.8)	13 553 (22.4)	286 (27.6)	1057 (26.1)
Diabetes	1944 (13.9)	8805 (13.0)	241 (23.3)	947 (23.4)
Hypertension	3196 (26.8)	13 388 (22.4)	653 (63.1)	2432 (60.1)
Chronic renal failure	1266 (9.1)	4737 (7)	0	0
Patients exposed to steroid treatments	10 664 (89.3)	27 029 (45.2)	977 (94.4)	2713 (67.1)

CU, chronic urticaria; BMI, body mass index. Statistically significant values are presented in bold, for comparison with age- and sex-matched controls (two-tailed). Patients with missing data: ^a864, ^b64, ^d33 984. ^cAge adjusted.

Table 2 The mean values of parathyroid hormone, vitamin D, calcium, albumin and IgE serum levels in blood tests performed during 2012–2017

	Patients with CU	General population	Osteoporosis with CU	Osteoporosis without CU
Vitamin D (ng dL ⁻¹) ^a	101.4 ± 37.5	103.4 ± 53.7	118.0 ± 30.1	86.0 ± 50.7
Calcium (g dL ⁻¹) ^b	9.43 ± 0.4	9.43 ± 0.4	9.44 ± 0.4	9.48 ± 0.4
Albumin (g dL ⁻¹) ^c	4.28 ± 0.3	4.28 ± 0.3	4.20 ± 0.3	4.19 ± 0.3
PTH (ng dL ⁻¹) ^d	51.6 ± 42.8	65.1 ± 83.8	46.2 ± 25.9	61.3 ± 55.4
IgE levels (IU) ^e	254.8 ± 625.8	43.7 ± 138.0	214.5 ± 351.3	92.4 ± 67.9

Data are presented as the mean ± SD. CU, chronic urticaria. Statistically significant values are presented in bold, for comparison with age- and sex-matched controls. Patients with available data: ^a3805, ^b39 615, ^c37 084, ^d1425, ^e20 684.

Table 3 Number of events: osteoporosis, vitamin D deficiency and calcium abnormalities

	Patients with CU n = 12 123	General population n = 60 453	Osteoporosis with CU n = 1035	Osteoporosis without CU n = 4046
Cohort total				
Osteoporosis	1035 (8.7)	4046 (6.8)	—	—
Incidence rate of osteoporosis, per 1000 PY (95% CI)	12.26 (11.53–13.03)	9.31 (9.03–9.61)	—	—
Hyperthyroidism	213 (1.9)	676 (1.2)	41 (4.0)	135 (3.3)
Hypothyroidism	3919 (7.1)	1141 (10.4)	244 (23.6)	783 (19.4)
Vitamin D deficiency	0	0	0	0
Hyperparathyroidism	116 (35.7)	421 (38.3)	40 (34.2)	159 (38.7)
Hypocalcaemia	21 (0.3)	158 (0.5)	1 (0.1)	23 (0.7)
Hypercalcaemia	19 (0.3)	110 (0.3)	3 (0.3)	41 (1.3)
Hypoalbuminaemia	235 (3.3)	1242 (4.1)	32 (4.0)	167 (5.6)
Follow-up (PY)	84 400	434 281	149	1098

Data are presented as n (%) unless stated otherwise, from the available data. CU, chronic urticaria; PY, person-years; CI, confidence interval. Statistically significant values are presented in bold, for comparison with age- and sex-matched controls.

blood tests performed in the study population during the study's observation years. Compared with the controls, patients with CU had significantly lower PTH serum levels. The IgE serum levels were increased in patients with CU in comparison with the controls (mean 254.8 ± 625.8 vs. 43.7 ± 138.0 IU, $P < 0.001$; peak 24 236 vs. 12 447 IU, $P < 0.001$). Lower PTH and higher IgE serum levels were observed in patients with osteoporosis and CU compared with both patients without CU and the general population.

The total follow-up times were 84 400 person-years for patients with CU and 434 281 person-years for controls. The incidences of osteoporosis were 12.26 [95% confidence interval (CI) 11.53–13.03] and 9.31 (95% CI 9.03–9.61) per 1000 person-years among patients with CU and controls, respectively. The attributable risk is 2.95 per 1000 person-years. The numbers of events, thyroid and parathyroid dysfunctions and other incidents of serum abnormalities in both the cases and controls are presented in Table 3. The mean time from the CU signal to the osteoporosis diagnosis was 14.34 ± 0.03 years (95% CI 14.29–14.40) in the CU group and 14.51 ± 0.01 years (95% CI 14.48–14.52) in the controls ($P < 0.001$). According to the univariate analysis, patients with CU had higher rates of osteoporosis, hyperthyroidism and hypothyroidism, and lower rates of hypocalcaemia and hypoalbuminaemia. The multivariate Cox

Table 4 Cox regression results for the association between the investigated risk factors and hazard ratios for osteoporosis

	Risk ratio	95% CI	P-value
Chronic urticaria	1.23	1.10–1.37	< 0.001
Age	1.07	1.06–1.07	< 0.001
Male sex	0.41	0.38–0.44	< 0.001
Corticosteroid exposure	1.67	1.53–1.83	< 0.001
Obesity	0.75	0.68–0.81	< 0.001
Smoking	1.09	1.01–1.21	0.023
Hyperthyroidism	1.22	0.96–1.55	0.10
Hypothyroidism	1.15	1.03–1.29	< 0.001

The data are adjusted for age, sex, corticosteroid exposure, obesity, smoking status, hyperthyroidism and hypothyroidism. P-values < 0.05 are significant.

regression analysis adjusted for age, sex, exposure to systemic corticosteroids, obesity, smoking and hyper- and hypothyroid disease revealed consistent results (Table 4).

The stratified analysis demonstrated that 1206 patients with CU and 31 280 controls had never been exposed to any systemic corticosteroids (oral, inhaled, injection, etc.), with 602 events of osteoporosis. In this subgroup, CU showed a significant association, with a 44% increase in risk for patients with osteoporosis compared with controls (hazard ratio 1.44, 95%

CI 1.10–2.17, $P < 0.001$). Finally, a sensitivity analysis where the outcome was syphilis did not reveal any significant differences between patients with CU and their matched control group (relative risk 1.05, 95% CI 0.24–4.74), thus arguing against the presence of surveillance bias.

Discussion

We investigated the association between CU and osteoporosis in a large community-based healthcare database. CU was associated with lower serum PTH, lower rates of hypocalcaemia and higher rates of osteoporosis. Patients with osteoporosis and CU were younger and more likely to be male, and had a higher prevalence of obesity than osteoporotic patients without CU, further strengthening the association between CU and osteoporosis. According to the temporal relation analysis, osteoporosis was observed earlier in the cohort of patients with CU than in the cohort of patients without CU. The association between CU and osteoporosis remained significant after controlling for age, sex, exposure to systemic corticosteroids, obesity, smoking and hyper- and hypothyroid disease, thus suggesting that CU alone is associated with osteoporosis. Lastly, the stratified analysis, which was performed in a subgroup of patients with no exposure to steroids, demonstrated a 44% increase in the risk for osteoporosis in patients with CU, while in the entire study population CU was associated with a 22% increase in the risk for osteoporosis. This observation emphasizes the role of CU in the risk for osteoporosis.

The validity of the CU diagnoses in the present study can be supported by several findings. The demographic features fit the epidemiological characteristics of CU, namely, female sex predominance and average age.¹ Moreover, patients with CU had a higher Charlson Comorbidity Index score, which is consistent with the growing concept of CU as a chronic, low-grade inflammatory condition. Healthcare services and drug-usage profiles of the present CU group were tested and found to be in accordance with the expected profile of CU that we reported recently.⁸ Taken collectively, the similarities, the correlation with previous epidemiological studies and the conservative case definition imply the high validity of our observation.

The notion that mast cells and their secreted products play a potential pathogenic role in bone loss is not new. Mast cell deficiency has been associated with low remodelling states, whereas their excess is associated with accelerated bone absorption.^{10,11} The production of bone cytokines by mastocytes in osteopenic and osteoporotic patients has been suggested to shift the balance of bone turnover towards increased bone resorption and decreased bone formation.^{12–19} Unfortunately, human studies addressing whether or not mast cell inhibition can be beneficial in osteoporosis are rare, and data evaluating bone mineral density or even fracture risk are limited.^{14,15} Therefore, a pathophysiological explanation for the observed higher prevalence of osteoporosis in patients with CU is currently lacking. We can only speculate about the

hypothetical roles of chronic inflammation and perhaps how the abnormalities of mast cells link these two chronic diseases.

Patients with CU have multiple potential risk factors for osteoporosis, including female predisposition, exposure to systemic corticosteroids and chronic inflammation. As our data stand, CU by itself may impose an added risk for osteoporosis on top of the known factors. As the best treatment strategy for osteoporosis is early intervention in the presence of risk factors, targeted screening for patients with CU should be considered in the appropriate clinical setting.

Our investigation explored a large community-based database and considered all underlying diagnoses and auxiliary test results. It is the first study of its kind designed to address the question of an association among CU, osteoporosis and the risk factors for osteoporosis. It reports real-life observations on CU, osteoporosis and relevant risk factors in a group of patients outside the hospital setting, and therefore it overcomes a potential selection bias of tertiary-centre-based investigations (Berksonian bias). However, this study does have some limitations. The case definition was based on digital data and could have resulted in an underestimation of the true frequency of CU. Subsequently, the general frequency of CU (0.27%) observed in the study was lower than the 0.5–5% that is usually reported.¹ Nevertheless, the conservative case definition we used markedly increased the study's specificity and thus reduced false diagnoses.

Naturally, exploring large datasets may amplify slight differences that can be detected even when they are of limited relevance in clinical practice, just as how our study demonstrated a subtle, yet significant, higher risk for osteoporosis in the population with CU. This observation is in accordance with the growing concept of CU as a chronic, low-grade inflammatory condition and has clinical applications from a public health point of view. Thus, despite the above limitations, the present study exposed important data on the association between CU and osteoporosis in patients with CU in a community setting. This group represents the majority of the patients who physicians encounter, and thus the efforts to improve the quality of CU care are supported.

In conclusion, our study adds important epidemiological evidence on the association between CU and osteoporosis. As early detection and treatment of osteoporosis are the best intervention, targeted screening is advised in patients with CU.

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